Electronic Submissions Program Update

March 22, 2004

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Discussion Points

- History – Significant Milestones
- Program Goals
- Submission & Review Tools
- Gateway Development Effort
- Adverse Event Reporting
- Secure Email Upgrade (Reg. Communication - attachments)
- Electronic Signature/Regulatory Correspondence Pilot
- Summary

History - Significant Milestones

- Establishment of ERSR program within CBER (5/96)
- First contemporary CBER Electronic Submission (CAPLA) – 8/96 - Amgen
- Implementation of Electronic Submission Standards 8/98
- Implementation of Electronic Submission Management Paradigm. Our present demo process – (8/98)
- Decision to make the roadmap.pdf file a central feature in all CBER electronic submission – 6/99 (This file, which is a correspondence history is the basis for the eCTD XML backbone)
- First electronic IND (received as part of CBER's eIND pilot program) 10/25/99 - Merck

History - Significant Milestones

- EDR
  - **Pilot – March 2000**
  - **Production – July 2000**
  - **ESM & eRouting – July 2002**
  - **New EDR Interface – Oct 2002 (all active electronic and paper applications represented in the EDR)**
  - **New EDR Interface – being developed**
- Receipt of Electronic only Biologic License Applications – June 2000

History - Significant Milestones

- Establish ESM and eRouting Pilot Program for INDs – August 2002
- Received first electronic regulatory amending submission with an electronic digital signature for review via secure email – September 2002
- Received first electronic only Original Submission of an IND – October 2002
- Role out of ESM and eRouting to CBER – October 2002
- Able to receive Blood Establishment Registration and Product listing – electronic only – (11/2002)

History - Significant Milestones

- Implemented electronic routing and direct data entry capability for electronic BLA's (3/2003)
- Developing necessary infrastructure to manage eCTD based submissions (3/2003)
- Implementation of Secure Email – Regulatory Communications with attachment up to 50 MB for all applications within the EDR (11/2003)
- Ability to electronically route and sign CBER Official Regulatory Correspondence (Pilot Started 12/2003)

History - Significant Milestones

- Capability to disseminate Official Regulatory Correspondence Electronically implemented (Pilot Started 12/2003)
- All CBER Official Regulatory Correspondence archived within the EDR (Pilot Started 12/2003)
- Able to receive Pre-Marketing adverse events via secure email (12/2003)

History - Significant Milestones

- Guidance Documents
  - January 1999; Guidance for Industry: Providing Regulatory Submissions in Electronic Format – General Considerations
  - November 1999; Guidance for Industry: Providing Regulatory Submission to the Center for Biologics Evaluation (CBER) in Electronic Format – Biologics Marketing Applications (BLA)
  - January 2001; Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Prescription Drug Advertising and Promotional Labeling
  - May 2001; Guidance for Industry: Providing Regulatory Submissions in Electronic Format - Postmarketing Expedited Safety Reports
  - March 2002; Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Investigational Drug Applications (IND)

History - Significant Milestones

Guidance Documents (continued)

- June 2003; Draft Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Postmarketing Periodic Adverse Drug Experience Reports
- August 2003; Draft Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Product Applications and Related Submissions
- October 2003; Draft Guidance for Industry: Providing Regulatory Submissions in Electronic Format - General Considerations
- To be Released; Guidance for Industry: Providing Regulatory Submissions to CBER in Electronic Format - Investigational Device Exemption (IDEs)

History - Significant Milestones

- WDK 5 Documentum upgrade starts – 3/2004
- Enterprise Architecture Business Processes Documentation Completed – target 5/2004
- First eCTD submission – xx/2004
- First eCTD-eIND – xx/2004
- Integration of CBER and CDER secure email paradigm - xx/2004
  - Starting with certificate central management (S/MIME)
- Begin Implementation of New FDA Gateway – xx/2004

Program Goals

- Assist the reviewer community in meeting PDUFA goals
- Provide reviewers with intuitive, standard presentations and tools
- Establish electronic submissions standards and guidance
- Provide the ability to manage all CBER submission types, starting with INDs, BLAs, and Promotional Labeling
- Enable CBER to meet their PDUFA, FDAMA and MDUFMA mandates and timelines
- Decrease administrative processing time
- Decrease processing time in order to facilitate reviewer access to regulatory submissions through the use of programmatic infrastructure

Submission & Review Tools

- Electronic Document Room (EDR)
  - Core system for CBER electronic submissions
  - Acts as the final submission and internal document repository/archive for all active submissions (i.e., paper and electronic)
  - Provides the user interface through which reviewers access, download, and review submissions
  - Interfaces to corporate databases for submission data (i.e., BIMS, RMS/BLA)

Submission & Review Tools

- Electronic Secure Messaging (ESM)
  - Provides a secure communications channel between CBER and Industry
  - Enables

1. **The submission of electronically signed and encrypted regulatory amendments to preexisting electronic applications in a fully automated fashion**
2. **Application based secure communication with Industry for all active paper and electronic submissions**
3. **The submission of Pre-Marketing Adverse Events**

Submission & Review Tools

- Electronic Signature
  - Digital signatures fully compliant with 21CFRPart 11
  - Utilizes Adobe and VeriSign certificates, with future plans for additional vendor support
  - Digital Signature being deployed to facilitate the signing, archiving and dissemination of regulatory correspondence

Submission and Review Tools

- E-Routing
  - Provides fully electronic workflow for the routing of IND and BLA submissions
  - Simple electronic forms (paper based forms presented as electronic formwork) presented to RPMs. These forms allow RPMs to perform direct data entry of regulatory information into corporate databases
  - Notifies reviewers of new submissions
  - Includes information extracted from pdf smart forms
    - 1571 item 11
    - 3500A the text that describes the actual adverse event

Adverse Event Reporting

- Premarketing Submissions
  - IND
  - IDE
- Implemented 12/03 – GeMCRIS
- Secure Email Delivery System
- Features pdf smart form technology
  - 1571 and 3500A on FDA Forms Webpage
  - Acrobat Reader 6.0 enabled
  - Data Extracted and Archived
  - Reviewer receives email with text of Adverse Event

Adverse Event Reporting

- GeMCRIS – Gene Modification Clinical Research Information System
- Collaborative Effort - NIH and FDA
- Database
  - Clinical Trials/Development
  - Safety Reporting
- FDA receives reports electronically via secure email conduit and sends data programmatically extracted from the forms for G&C clinical trails to the NIH via email

Adverse Event Reporting

- PDF technology
- Reasoning
  - Leverage functioning infrastructure
  - Enable Academic Institutes into venture in this space
    - Email common to all organizations
    - CBER can issue S/MIME certificates to Academic Institutions
    - Acrobat Reader enabled forms
      - Fill-able
      - Sign-able

Adverse Event Reporting

- Reviewers (i.e. RPM, Clinical, and Product Reviewer noted in BIMs) notified via there Outlook accounts of the arrival of a secure email delivered Adverse Event
- EDR archival repository
- Forms archived in appropriate application folder
- Reviewers can easily access AE clinical development information even for paper-based submissions
- Every active IND and IDE within CBER eligible
- Virtually no infrastructure/programming cost to utilize programmatic capabilities

Secure Email

- Options
  - Delivery of amending submissions to previously existing electronic submissions
  - Regulatory Communications
- Highlighting 2nd Option of Paradigm
- Regulatory Communications
- Scope
  - All Active Applications
  - Text and attachments
  - Attachments – 50 megabytes
  - Not for delivery of amendments

Secure Email

- Use
  - Discussions with applications review team
    - Paper based submissions and electronic submissions
  - Sending of Attachments for Informal Review
    - Replace fax
    - Information automatically archived
    - Reviewers notified of the receipt of a secure email message
    - Reviewers can send secure email messages
    - RPM = Gate Keeper
    - Do not incorporate any FDA forms or the roadmap.pdf file.
    - Do not incorporate the following form filenames for 1571s or 356hs

Official Regulatory Correspondence

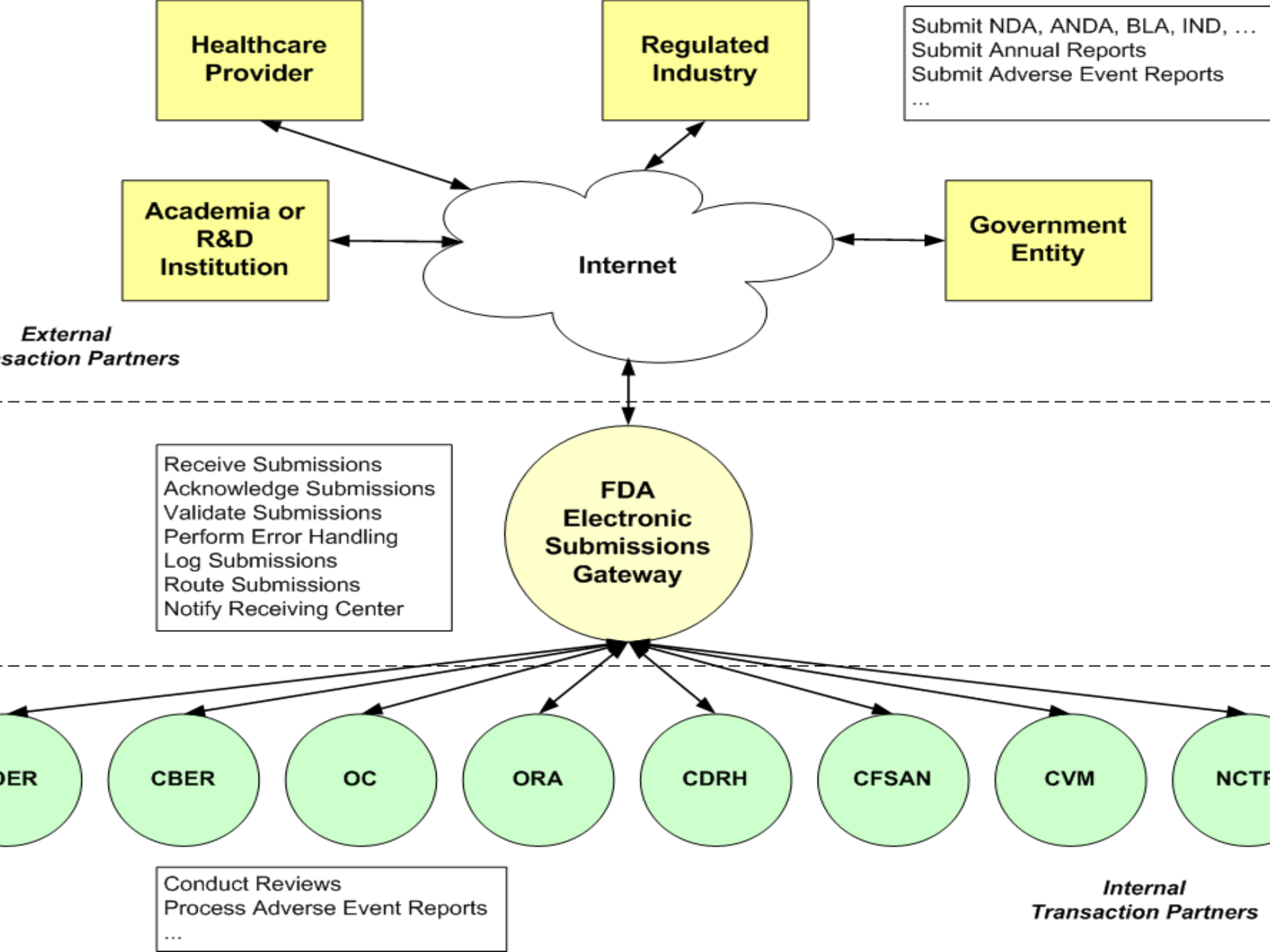
- New Pilot Program
- Scope: Electronically Signing and Archiving Official Regulatory Correspondence (i.e., Admin and Review) and archiving them within the EDR
- Intention: To send a Sponsor an electronic copy of the review or administrative correspondence for their application if a secure email connection is available
- Office of Cellular Tissue and Gene Therapy
- Will be expanded to all Product Review Offices within CBER

FDA Gateway Program

- Project Leads
  - Project Officer – Mark Gray OC/OCIO
  - Program Manager – Michael B. Fauntleroy CBER/OD
  - Technical Lead – Joseph Montgomery CBER/OIM

FDA GATEWAY

- New Gateway project
- Web enabled
- Ultimately will replace present ESTRI Gateway
- Project Team
- Participants
  - CBER
  - CDER
  - CDRH
  - CFSAN
  - OC/OCIO
  - ORA


Healthcare Provider
Regulated Industry
Submit NDA, ANDA, BLA, IND, …
Submit Annual Reports
Submit Adverse Event Reports
…
Academia or R&D Institution
Internet
Government Entity
External
saction Partners
Receive Submissions
Acknowledge Submissions
Validate Submissions
Perform Error Handling
Log Submissions
Route Submissions
Notify Receiving Center
FDA Electronic Submissions Gateway
DER
CBER
OC
ORA
CDRH
CFSAN
CVM
NCTR
Conduct Reviews
Process Adverse Event Reports
…
Internal
Transaction Partners

FDA Gateway

- Project Started 9/2003
- Documents Generated
  - System Requirements Specification - 12/18/2003
  - System Architecture Specification – 12/18/2003
  - SHARE Project Plan – 12/18/2003
  - Statement of Work
    - Draft – 12/18/2003
    - Finalized – 2/13/2004
    - Contract Staff Revisions – 3/15/2004
  - RFP – xx/2004?
  - Contract Awarded - xx/2004

FDA Gateway

- Focus
  - Receiving Submissions and Amendments
    - **INDs**
    - **BLAs**
    - **IDEs**
    - **eCTDs**
    - **etc.**
  - Adverse Event Reporting
    - **AERS**
    - **VAERS**
    - **BAERS**
    - **etc.**
  - External Communications

FDA Gateway

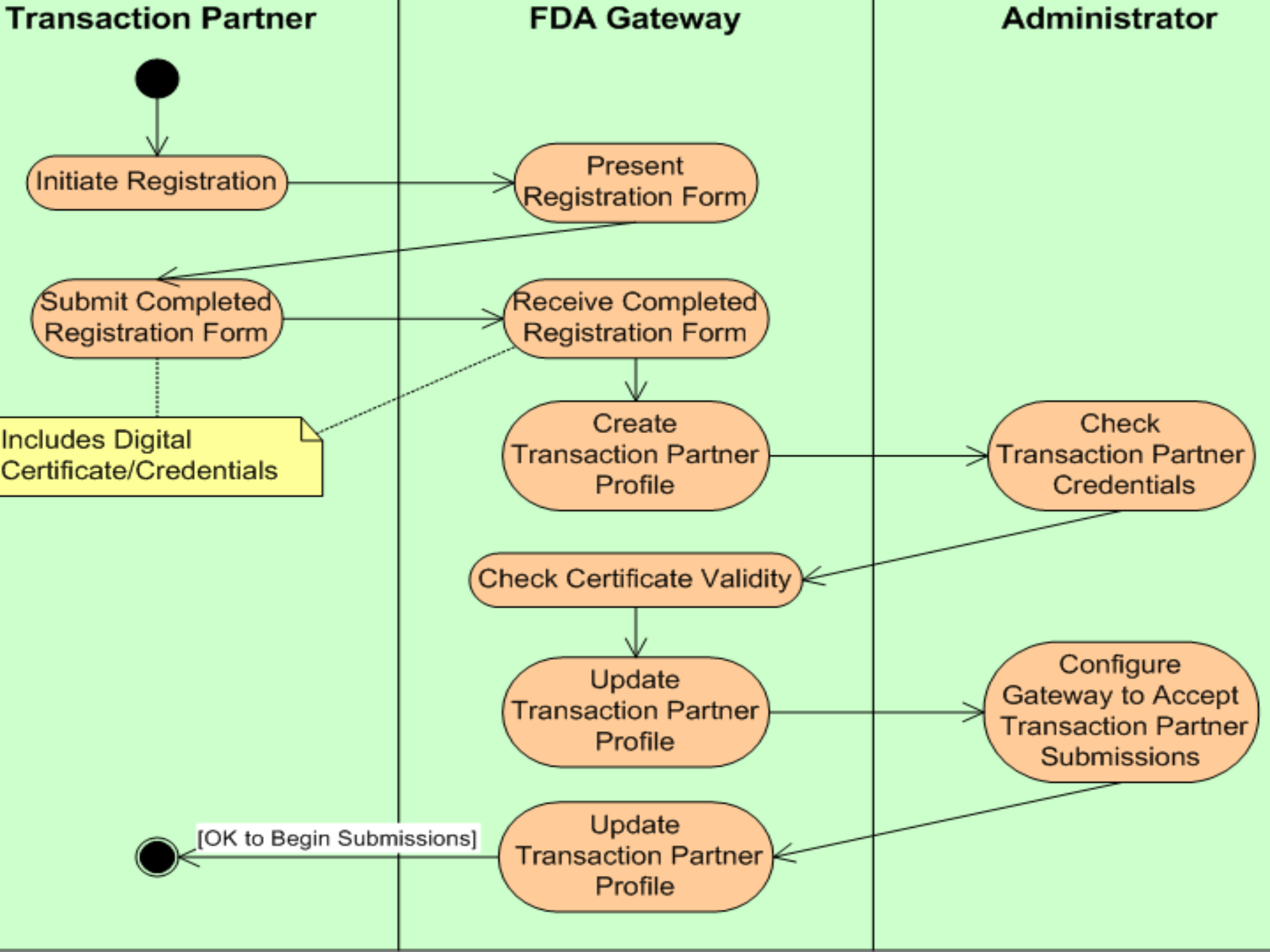
- Incremental Development Effort
  - Four Increments
    - **Deploy Core Elements of Gateway**
    - **First Increment – enable receipt of electronic applications and adverse event reporting to CBER an CDER**
    - **Second Increment – enable all non-PDUFA Center to receive electronic submissions of all types**
    - **Third Increment – enable interaction with external Gateway Interfaces**

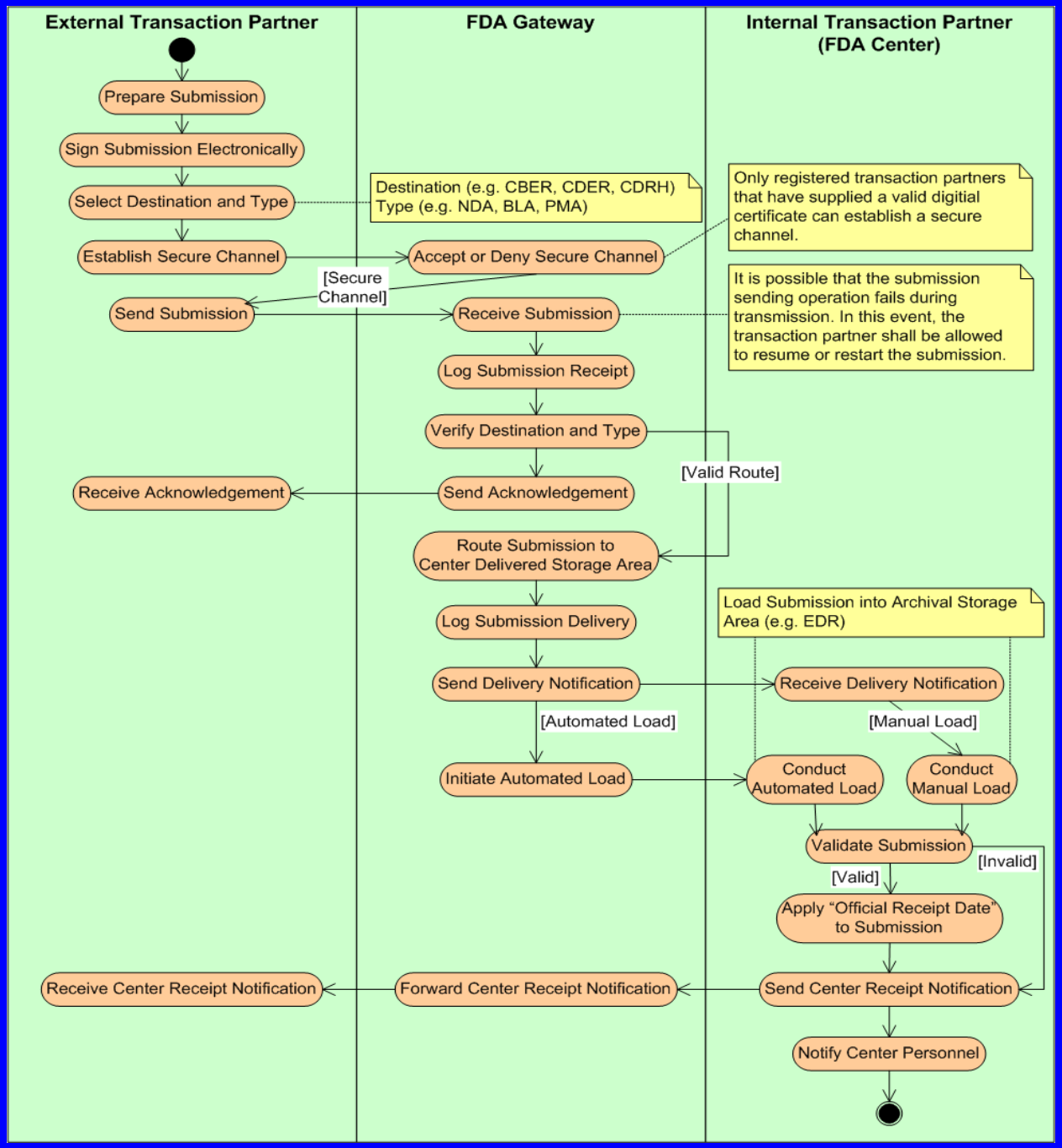
FDA Gateway

- Employ the use of an Applet/Servlet
- Transaction Partners
- Configurable Gateway
- Center Designations/Application Types
- OC-3 line
- Shall Support Multiple Applications/Submissions Sessions
  - Individual files up to 100 megabyte
  - 100 gigabyte application
  - 25 1-5 gigabyte applications
  - AERS submissions

FDA Gateway

- AERS/VAERS/BEARS Reporting
  - Average Number per Day 2K, Peak number 4K
  - Average report size under 50 Kilobytes
  - Attachment max size 50 megabyte
- Employ
  - Redundant Architecture and Technologies
  - Reliable Technologies
  - Redundant Systems Components
- Dependable (24x7x365)


Transaction Partner
FDA Gateway
Administrator
Initiate Registration
Present Registration Form
Submit Completed Registration Form
Receive Completed Registration Form
Includes Digital Certificate/Credentials
Create Transaction Partner Profile
Check Transaction Partner Credentials
Check Certificate Validity
Update Transaction Partner Profile
Configure Gateway to Accept Transaction Partner Submissions
[OK to Begin Submissions]
Update Transaction Partner Profile


External Transaction Partner
FDA Gateway
Internal Transaction Partner (FDA Center)
Prepare Submission
Sign Submission Electronically
Select Destination and Type
Destination (e.g. CBER, CDER, CDRH)
Type (e.g. NDA, BLA, PMA)
Only registered transaction partners that have supplied a valid digitial certificate can establish a secure channel.
Establish Secure Channel
Accept or Deny Secure Channel
[Secure Channel]
Send Submission
Receive Submission
It is possible that the submission sending operation fails during transmission. In this event, the transaction partner shall be allowed to resume or restart the submission.
Log Submission Receipt
Verify Destination and Type
[Valid Route]
Receive Acknowledgement
Send Acknowledgement
Route Submission to Center Delivered Storage Area
Load Submission into Archival Storage Area (e.g. EDR)
Log Submission Delivery
Send Delivery Notification
Receive Delivery Notification
[Automated Load]
[Manual Load]
Initiate Automated Load
Conduct Automated Load
Conduct Manual Load
Validate Submission
[Invalid]
[Valid]
Apply "Official Receipt Date" to Submission
Receive Center Receipt Notification
Forward Center Receipt Notification
Send Center Receipt Notification
Notify Center Personnel

Summary

- CBER is the first Center to accept fully electronic regulatory documents with digital signatures
- CBER is the first Center to utilize fully automated submission processing (ESM)
- CBER is the first Center to receive regulatory submissions without paper or electronic media – just bits and bytes
- The EDR coupled with ESM and e-Routing form a complete set of robust review tools that decrease regulatory processing time and thereby facilitate the reviewers access to submission information. These tools were developed in conjunction with the review community
- CBER has established a low to no cost electronic adverse events reporting paradigm that features the use of pdf smart forms
- CBER is the lead Center for the Development of the New FDA Gateway

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